Prodromal – Very Early Symptoms of PD

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Prodromal PD

- Definition: The stage at which individual does not meet criteria for PD diagnosis (pre-diagnosis), with higher than normal risk for developing PD, and has non-motor symptoms that are impactful to quality of life. This is also referred to as the long latent phase of PD.

- Does not fulfill diagnostic criteria – bradykinesia + 1 other motor sign
  - Motor features: Bradykinesia (slowness of movement), rigidity, tremor, and postural instability.
Clinical non-motor markers of prodromal PD

The list of prodromal markers have now been expanded:

- Hyposmia (diminished or loss of sense of smell)
- Constipation
- REM sleep behavior disorder (RBD) (active dreams)
- Mood disorders (anxiety/depression)
- Erectile dysfunction
- Somnolence
- Orthostatic hypotension
- Urinary dysfunction
- Abnormal DAT/SPECT imaging study
- Cognitive dysfunction
Hyposmia

- **Anosmia** - Loss of smell; **Hyposmia** – impaired sense of smell.
- Most common, best characterized non-motor feature.
- 80% of patients with Hyposmia have Lewy body pathology.
- Standard tests such as 12-item Brief Smell Identification Test (B-SIT).
- Affects taste, weight loss.

(Michaeljfox.org, 2021)
Constipation

- Defined as infrequent stools, difficulty with stool passage.
- First and most common disabling non-motor symptom during prodromal phase.
- Pathological alpha-synuclein inclusions can be detected in the GI tract up to 20 years before diagnosis.
- Disabling non-motor symptom because it causes bloating, discomfort, and nausea.
- Honolulu – Asia Aging Study – symptoms to development of PD symptoms ~ 10 years, diagnosis ~ 12 years.
Rem Behavior Disorder (RBD)

- Characterized by dream enacting behavior, vocalizations, limb movements, usually related to unpleasant dreams.
- Loss of REM sleep muscle atonia
- Marker for prodromal degeneration or secondary to patients with PD.
Motor markers

- Unified Parkinson’s disease Rating Scale
- Abnormal 4.5 years before diagnosis
- First signs – voice and face akinesia
- Later signs –
  - Rigidity
  - gait abnormalities
  - limb bradykinesia
  - tremor

(Lewis et al., 2020)
Imaging markers – DAT/SPECT scan

- Dopamine transporter scan to assess for striatal dopaminergic uptake
- Decreased uptake in patients with PD

(Calle, et al., 2019)
Clinical PD Pathway and Determinant of Risks

(Di Virgilio, 2016)
Pre-diagnostic phase of PD

- Risk phase
  - Markers
    - Genetic markers
    - Environment
    - Personality?
    - Substantia nigra hyper-echogenicity

- Preclinical phase
  - Markers
    - None yet validated
    - Blood, CSF and tissue biomarkers?
    - Imaging markers?

- Prodromal phase
  - Markers (examples)
    - REM sleep behaviour disorder
    - Autonomic dysfunction
    - Olfactory dysfunction
    - Depression
    - Somnolence
    - Imaging abnormalities
    - Slight motor signs

- Clinical PD
  - >10 years

- Neurodegeneration
  - Non-motor symptoms
    - Slight motor signs
  - Clinical PD
Course of progression and Impact

(Mantri & Morley, 2016)
What does all this mean to you?

- Early recognition helps identify patients for clinical trials for neuroprotective therapies.
- Wide therapeutic index window
- No symptomatic medications
- Improves prognosis counseling
- Clinical trials for drug therapy with hope to preserve neuronal tissue (possible interventions for disease modifying therapy)
  - Clinicaltrials.gov
- Consideration for dopaminergic therapy
- Neuro-rehabilitation services (PT, OT, ST) is valuable in preservation of motor function and independence
References


